Pharmacogenetics 2000, **10**:5–10 *Original article*

CYP2D6 ultrarapid metabolizer genotype as a potential modifier of smoking behaviour

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Received 11 November 1998; accepted 6 May 1999

Some 3–10% of Caucasians are deficient in CYP2D6 metabolism (poor metabolizers), due to inheritance of two defective alleles, whereas amplification of the *CYP2D6* gene results in ultrarapid metabolism in 1–2% of Caucasian populations. To examine the possible association between *CYP2D6* polymorphism and individual smoking behaviour, we analysed the prevalence of *CYP2D6* genotypes among 292 long-term heavy smokers, 382 individuals with more variable smoking histories, and 302 never-smokers. The prevalence of ultrarapid metabolizers in heavy smokers (7.9%) was twofold compared to individuals with variable smoking habits (3.7%; odds ratio 2.3, 95% confidence interval 1.2–4.4), and fourfold compared with never-smokers (2.0%) (odds ratio 4.2, 95% confidence interval 1.8–9.8). The frequency of poor metabolizer genotype was approximately 2%, in each smoker group. However, when men and women were studied separately, the prevalence of poor metabolizer genotype was higher in male never-smokers (3.6%) than in variable smokers (2.7%) and heavy smokers (2.2%). Moreover, a trend test, adjusted by age, gender and cancer status, revealed a significant trend for the increased tobacco usage with increased metabolic capacity. Our results are in agreement with the assumption that increased CYP2D6 activity may contribute to the probability of being addicted to smoking. Pharmacogenetics 10:5–10 © 2000 Lippincott Williams & Wilkins

Keywords: CYP2D6, genotype, polymorphism, smoking

Introduction

Nicotine psychopharmacology is thought to be a key factor in tobacco dependence. Similar to many other addictive drugs, nicotine is known to exert its reinforcing effects through activation of the mesolimbic dopaminergic pathway (Corrigall, 1991; Stolerman & Shoaib, 1991; Dani & Heinemann, 1996). Previously, it has been hypothesized that one of the cytochrome P450 enzymes, CYP2D6, might modify tobacco dependence by catalysing oxidation of nicotine to cotinine (Cholerton *et al.*, 1994). However, recent studies suggest that CYP2D6 may have a minor role in the metabolism of nicotine (Benowitz *et al.*, 1996; Cholerton *et al.*, 1996; Messina *et al.*, 1997). Interestingly, based on their studies in rats, Niznik *et al.* (1990) suggested that CYP2D6 is related to dopamine transporter, and is involved in the catabolism and processing of neurotransmitters subsequent to their reuptake into target cells. The ability to bind to dopamine transporters has previously been shown to play a major role in the reinforcing effects of cocaine and some other addictive drugs (Johanson & Fischman, 1989; Woolverton & Johnson, 1992). On the other hand, human CYP2D6 was recently found to exhibit strong ability to convert endogeneous and exogeneous tyramine to dopamine (Hiroi *et al.*, 1998). The involvement of CYP2D6 in signal transduction in the dopaminergic pathway offers an alternative pathway by which it may modify individuals' smoking behaviour.

Homozygosity for recessive defective alleles of the *CYP2D6* gene results in poor metabolizer phenotype

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in 3–10% of Caucasians (Alván *et al.*, 1990; Daly *et al.*, 1996). The most common defective alleles consist of deletion of the entire gene (*CYP2D6*5* allele) and the two point mutations resulting in *CYP2D6*3* and *CYP2D6*4* alleles (Daly *et al.*, 1996). These alleles comprise approximately 90% of the poor metabolizer phenotype associated variants of *CYP2D6*. More recently, *CYP2D6* alleles representing duplication/amplification of the *CYP2D6* gene have also been described. In Caucasians, amplified alleles consist almost solely of duplications of the functional *CYP2D6*1* or *CYP2D6*2* genes (Johansson *et al.*, 1993; Ingelman-Sundberg, 1999), but rare duplication of the defective *CYP2D6*4* allele has also been detected (Løvlie *et al.*, 1996; Sachse *et al.*, 1997). Individuals who have inherited more than two copies of functional *CYP2D6* gene have a higher CYP2D6 enzyme activity than those with the prevalent extensive metabolizer genotype (one or two functional genes), and are consequently designated as ultrarapid metabolizers. Overall, the frequency of the duplicated alleles seems to vary widely between populations of different ethnic origins (Ingelman-Sundberg, 1999). In Scandinavian populations, the frequency of ultrarapid metabolizers has been reported to be 1–2% (Dahl *et al.*, 1995; Bathum *et al.*, 1998).

Several studies have reported on the role of *CYP2D6* polymorphism in tobacco addiction, with conflicting results. Turgeon *et al.* (1995) reported that the poor metabolizers were under-represented among smokers compared with the nonsmokers, supporting the hypothesis that poor metabolizer individuals would be less easily addicted to smoking. Subsequently, no significant difference was observed in the prevalence of *CYP2D6* genotypes between smokers and nonsmokers by Cholerton *et al.* (1996). More recently, however, the same group concluded that although *CYP2D6* status seems not to affect a person's probability of starting to smoke, it may modify the smoking behaviour among smokers (Boustead *et al.*, 1997). The *CYP2D6* ultrarapid metabolizer genotypes were not studied in the above studies.

We examined further the possible role of *CYP2D6* in individual variations in tobacco dependence, by analysing the *CYP2D6* genotype distribution, including the ultrarapid metabolizer genotype, in three groups with different smoking habits. The first group consisted of long-term persistent smokers, who had smoked more than 20 cigarettes per day for at least 20 years. The second group included individuals with variable smoking habits, i.e. smokers who had smoked fewer than 20 cigarettes per day and/or less than 20 years together with ex-smokers. The last group comprised individuals who had never smoked.

Materials and methods

Study populations

Altogether 976 individuals, 391 with cancer and 585 without cancer, were included in the study. Most of the non-cancer individuals were 67-year-old individuals living in the south-western area of Finland, while the cancer patients were enrolled from previous studies on cancer prevention and molecular epidemiology of lung cancer. The details of the design and main results of the cancer prevention study have been published elsewhere (ATBC Cancer Prevention Study Group, 1994). Participants for this study were men who had been diagnosed with a cancer of the lungs or urinary bladder, and individuals who controls were free of cancer at the time of blood sampling. The patients in the study on molecular epidemiology of lung cancer were all individuals who had been admitted to Helsinki University Hospital during 1988–96 for surgical pulmonectomy or lobectomy due to suspected, operable cancer (Saarikoski *et al.*, 1998).

All the study individuals were interviewed in detail for their smoking histories and divided into three groups according to smoking habits. The first group comprised 292 long-term persistent smokers who had smoked more than 20 cigarettes per day (mean 26 ± 10) for at least 20 years. The variable smokers group ($n = 382$) included 185 individuals who had smoked fewer than 20 cigarettes per day (mean 12 ± 4) and/or less than 20 years, and 197 ex-smokers from whom detailed smoking histories were not available. Among the lung cancer patients, ex-smokers who had quit smoking for less than 3 years earlier were included in the smoker category, since their symptoms during the period of suspicion and diagnosis of lung cancer may have forced them to quit. The third group consisted of 302 never-smokers. The mean age was 58 ($\pm$ 7) years for the long-term persistent smokers, 63 ($\pm$ 9) years for the individuals with variable smoking habits, and 62 ($\pm$ 11) years for the never-smokers. A minority of the long-term smokers (6%) and variable smokers (22%) were women, whereas they prevailed in the never-smoker group (73%).

Genotype analyses

Lymphocyte DNA was extracted by standard techniques from 10 ml of peripheral blood collected into ethylenediaminetetraacetic acid or heparin tubes. The *CYP2D6* genotype analysis used detected several variant alleles in addition to the wild-type allele *CYP2D6*1* (Daly *et al.*, 1996). Briefly, the amplified allele (*CYP2D6*2xN*), deleted allele (*CYP2D6*5*), and the loss of enzyme activity allele (*CYP2D6*16*), were

studied by Southern blotting analysis as described by Johansson *et al.* (1993), whereas the deficient *CYP2D6*4* and *CYP2D6*3* alleles were analysed by polymerase chain reaction-based methods as described by Smith *et al.* (1992) and Hirvonen *et al.* (1993), respectively. Individuals having inherited a defective allele together with a wild-type or an amplified allele were considered as extensive metabolizers. Although some of the individuals in this group could actually have had an amplified defective allele together with a wild-type allele, that does not affect the interpretation of the results since they would anyway be categorized as extensive metabolizers. Poor metabolizers were homozygous for defective alleles while ultrarapid metabolizers were heterozygous for the wild-type and amplified alleles.

Statistical analyses

Odds ratios and 95% confidence intervals were calculated with the two-sided Mantel-Haenszel method. The proportional odds model (McCullagh & Nelder, 1994) was used to analyse smoking as three-category ordinal response.

Results

As shown in Table 1, the amplified *CYP2D6* alleles, which based on the intensities of the hybridization signals in the Southern blotting analysis were all gene duplications, were significantly more prevalent in the long-term heavy smokers (4.2%) than in the never-smokers (1.2%; $P = 0.009$). In contrast, the other alleles were quite similarly distributed in the study groups.

The distribution of *CYP2D6* genotypes is shown in Table 2. The prevalence of ultrarapid metabolizers in heavy smokers (7.9%) was twofold compared with individuals with variable smoking habits (3.7%; odds ratio 2.3, 95% confidence interval 1.2–4.4), and fourfold compared with never-smokers (2.0%; odds ratio 4.2, 95% confidence interval 1.8–9.8) (Table 2). In contrast, the frequency of poor metabolizer genotype was about 2%, in each smoker group. To avoid overlapping with the groups of variable smokers and heavy smokers, the genotype distribution was analysed among the variable smokers by excluding individuals who had smoked 16–19 cigarettes per day, i.e. very close to the cut-off point for the heavy smokers ($n = 20$). Exclusion of these individuals did not affect the outcome of the analysis (data not shown).

Since about 40% of the study individuals were cancer patients and there were clearly more women among nonsmokers than among smokers, we also performed separate analyses to non-cancer individuals and men to exclude the possible confounding caused by the disease status and gender.

When the analyses were restricted to the non-cancer individuals ($n = 585$), the outcomes were not significantly different from those observed for the whole study set. In this subpopulation, the ultrarapid metabolizer genotype frequency was 2.3% in the never-smokers, 3.8% in the variable smokers and 12.9% in the heavy smokers, respectively (Table 2). Among the heavy smokers, there was thus an almost fourfold frequency of the ultrarapid metabolizer genotype compared to the intermediate smoking group (odds ratio 3.7, 95% confidence interval 1.5–8.8), and more than sixfold frequency compared with nonsmokers (odds ratio 6.2, 95% confidence interval 2.5–15.7). None of the heavy smokers had the poor metabolizer genotype, whereas 2.3% of the individuals with variable smoking habits and 2.1% of the never-smokers were poor metabolizers.

When only men were included in the analysis, the frequencies of ultrarapid metabolizer and poor

Table 1. Distribution of *CYP2D6* alleles among groups with different smoking habits

	Never smokers (n = *302*)		*Variable smokers* (n = *383*)		*Heavy smokers* (n = *292*)	
Allele	n	*Frequency*	n	*Frequency*	n	*Frequency*
*CYP2D6*1*	492	0.815	614	0.803	467	0.801
*CYP2D6*2* × *N*[a]	7	0.012	19	0.025	25	0.042
*CYP2D6*3*	13	0.022	20	0.026	14	0.024
*CYP2D6*4B*	47	0.078	60	0.079	42	0.072
*CYP2D6*4C*	30	0.050	22	0.029	20	0.034
*CYP2D6*5*	10	0.017	19	0.025	13	0.022
*CYP2D6*10*	2	0.003	8	0.010	3	0.005
*CYP2D6*16*	2	0.003	2	0.003	0	–

[a]Denoting duplication/amplification of *CYP2D6*1*, *CYP2D6*2* or *CYP2D6*4*.

Table 2. Distribution of *CYP2D6* genotypes among groups with different smoking habits

	Never-smokers		*Variable smokers*		*Heavy smokers*	
Study group	n	%	n	%	n	%
All subjects ($n = 976$)						
PM	7	2.3	8	2.1	6	2.1
EM[a]	289	95.7	360	94.2	263	90.0
UM	6	2.0	14	3.7	23[b,c]	7.9
Males ($n = 656$)						
PM	3	3.6	8	2.7	6	2.2
EM[a]	79	95.2	277	93.3	247	89.5
UM	1	1.2	12	4.0	23[d,e]	8.3
Non-cancer ($n = 585$)						
PM	6	2.3	5	2.1	0	–
EM[a]	252	95.4	222	94.1	74	87.1
UM	6	2.3	9	3.8	11[f,g]	12.9

PM, poor metabolizer; EM, extensive metabolizer; UM, ultrarapid metabolizer
[a]Reference category. [b]Heavy smokers versus variable smokers; OR = 2.3 (95% CI = 1.2–4.4). [c]Heavy smokers versus never-smokers; OR = 4.2 (95% CI = 1.8–9.8). [d]Heavy smokers versus variable smokers; OR = 2.2 (95% CI = 1.1–4.4). [e]Heavy smokers versus never-smokers; OR = 7.4 (95% CI = 1.3–41.6). [f]Heavy smokers versus variable smokers; OR = 3.7 (95% CI = 1.5–8.7). [g]Heavy smokers versus never-smokers; OR = 6.2 (95% CI = 2.5–15.7). OR, odds ratio; CI, confidence interval.

metabolizer genotypes in the three groups with different smoking habits remained almost unchanged (Table 2). In this subpopulation, 8.3% of the heavy smokers, 4.0% of the variable smokers and 1.2% of the nonsmokers were ultrarapid metabolizers. Thus, the prevalence of the ultrarapid metabolizer genotype in male heavy smokers was twice as high as that among men with variable smoking habits (odds ratio 2.2, 95% confidence interval 1.1–4.4), and more than sevenfold compared to that of the nonsmoker men (odds ratio 7.4, 95% confidence interval 1.3–41.6). A tendency towards a lower prevalence of the poor metabolizer genotype was seen in relation to increasing tobacco smoke dose; the poor metabolizers were most prevalent in never-smokers (3.6%) followed by variable smokers (2.7%) and heavy smokers (2.2%).

We also applied the proportional odds model (McCullagh & Nelder, 1994) to analyse smoking as three-category ordinal response. Age, gender, cancer status, original study where the observations were obtained and the three-category metabolizing activity were used as explanatory variables. The results appeared similar to those presented in Table 2, and a significant trend ($P < 0.05$) was observed for the increased tobacco usage with increased metabolic capacity.

Since we (Hirvonen *et al.*, 1993) and others (d'Errico *et al.*, 1996; Rostami-Hodjegan *et al.*, 1998) have previously observed a modifying role for *CYP2D6* genotype in individual lung cancer risk, this issue was studied further. In the present study, we did not find any association between the CYP2D6 status and susceptibility to lung cancer, however. The frequencies of the ultrarapid metabolizer and poor metabolizer genotypes were 4.2% and 2.5% in the lung cancer patients, and 4.4% and 1.9% in the non-cancer individuals, respectively.

Discussion

In the present study, the working hypothesis was that individuals having *CYP2D6* poor metabolizer genotypes would be under-represented among heavy smokers, whereas those with ultrarapid metabolizer genotypes were assumed to have increased probability of becoming addicted to smoking. In agreement with this, the prevalence of *CYP2D6* ultrarapid metabolizer genotype was fourfold among long-term chronic smokers and twofold among individuals with variable smoking histories compared with never-smokers. Although we did not observe any overall decrease in the prevalence of poor metabolizers among the heavy smokers in this study, a non-significant under-representation of poor metabolizers was observed among the smoking non-cancer individuals and among men. Furthermore, a trend test for the whole study population revealed a significant

trend for the increased tobacco usage with increased metabolic capacity when adjusted by age, gender and cancer status.

Turgeon *et al.* (1995) showed a clear over-representation of poor metabolizers among nonsmokers compared with smokers, whereas lack of association was subsequently reported by Cholerton *et al.* (1996). In the latter study, individuals were divided between smokers having smoked more than five cigarettes per day for at least 5 years and non-smokers including ex-smokers who had quit smoking at least 10 years prior to the study. In the present study, long-term heavy smokers, who had smoked more than 20 cigarettes per day for at least 20 years, were selected to constitute the most strongly addicted group. The prevalence of ultrarapid metabolizer genotypes was much higher in this group than in the group of individuals with variable smoking habits (i.e. smokers who had smoked fewer than 20 cigarettes per day and/or less than 20 years, and ex-smokers) in each subgroup. Exclusion of variable smokers who smoked 16–19 cigarettes per day did not influence the outcome of the analyses.

Increased susceptibility of ultrarapid metabolizer individuals to being addicted to smoking may result in greater use of cigarettes and higher exposure to tobacco carcinogens. This could consequently contribute to increased risk of lung cancer. To our knowledge, studies on the association between ultrarapid metabolizer genotype and lung cancer susceptibility have not been published. In contrast, the proposed association between *CYP2D6* poor metabolizer genotype and decreased risk of lung cancer has been actively studied, with contradictory results (d'Errico *et al.*, 1996; Rostami-Hodjegan *et al.*, 1998). In this study, we did not observe any deviations in the *CYP2D6* poor metabolizer or ultrarapid metabolizer genotype frequencies between lung cancer cases and non-cancer individuals. However, since this kind of study requires detailed information about smoking habits, the non-cancer population we were able to recruit does not represent a random sample of general population. For example, a great proportion of this population consisted of heavy smokers from the ATBC Cancer Prevention Study (1994) who had not developed smoking related cancers. The present study population does therefore not allow optimal examination of the potential relationship between *CYP2D6* polymorphism and lung cancer.

In addition to CYP2D6, genetic deficiency in CYP2A6, which is the major nicotine *C*-oxidase (Messina *et al.*, 1997), was recently associated with smoking behaviour; smokers carrying defective *CYP2A6* alleles appeared to consume fewer cigarettes (Pianezza *et al.*, 1998). However, the method used for *CYP2A6* genotyping by Pianezza and coworkers (Fernandez-Salguero *et al.*, 1995) was subsequently suggested to give erroneous results (Oscarson *et al.*, 1998), and their findings need to be confirmed in future studies.

Taken together, in this study the prevalence of *CYP2D6* ultrarapid metabolizer genotype was significantly higher among heavy smokers than among smokers with variable smoking habits and among never-smokers. This supports the hypothesis that CYP2D6 may be involved in the biological processes influencing smoking behaviour. It must be kept in mind, however, that multiple psychopharmacological effects contribute to tobacco dependence, and the potential role of CYP2D6 in this complex process needs to be carefully evaluated in future studies before any strict conclusions can be drawn.

Acknowledgements

This work was supported in part by grants from Yrjö Jahnsson Foundation (3942), the Academy of Finland (29456), and Finnish Work Environment Fund (97179), and by a contract (N01-CN-45165) with NCI (National Cancer Institute, USA).

References

Alván G, Bechtel P, Iselius L, Gundert-Remy U. Hydroxylation polymorphisms of debrisoquine and mephenytoin in European populations. *Eur J Clin Pharmacol* 1990; **39**:533–537.

ATBC Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New Engl J Med* 1994; **330**:1029–1035.

Bathum L, Johansson I, Ingelman-Sundberg M, Hørder M, Brøsen K. Ultrarapid metabolism of sparteine: frequency of alleles with duplicated *CYP2D6* genes in a Danish population as determined by restriction fragment length polymorphism and long polymerase chain reaction. *Pharmacogenetics* 1998; **8**:119–123.

Benowitz NL, Jacop PI, Perez-Stable E. CYP2D6 phenotype and the metabolism of nicotine and cotinine. *Pharmacogenetics* 1996; **6**:239–242.

Boustead C, Taber H, Idle JR, Cholerton S. *CYP2D6* genotype and smoking behaviour in cigarette smokers. *Pharmacogenetics* 1997; **7**:411–414.

Cholerton S, Arpanahi A, McCracken N, Boustead C, Taber H, Johnstone E, *et al*. Poor metabolisers of nicotine and *CYP2D6* polymorphism [letter]. *Lancet* 1994; **343**:62–63.

Cholerton S, Boustead C, Taber H, Arpanahi A, Idle JR. *CYP2D6* genotypes in cigarette smokers and non-tobacco users. *Pharmacogenetics* 1996; **6**:261–263.

Corrigall WA. Understanding brain mechanisms in nicotine reinforcement. *Br J Addiction* 1991; **86**:507–510.

Dahl M-L, Johansson I, Bertilsson L, Ingelman-Sundberg M, Sjöqvist F. Ultrarapid hydroxylation of debrisoquine in a Swedish population. Analysis of the molecular genetic basis. *JPET* 1995; **274**:516–520.

Daly AK, Brockmöller J, Broly F, Eichelbaum M, Evans WE, Gonzalez FJ, *et al*. Nomenclature for human *CYP2D6* alleles. *Pharmacogenetics* 1996; **6**:193–201.

Dani JA, Heinemann S. Molecular and cellular aspects of nicotine abuse. *Neuron* 1996; **16**:905–908.

d'Errico A, Taioli E, Chen X, Vineis P. Genetic polymorphisms and the risk of cancer, a review of the literature. *Biomarkers* 1996; **1**:149–173.

Fernandez-Salguero P, Hoffman SMG, Cholerton S, Mohrenweiser H, Raunio H, Rautio A, *et al*. A genetic polymorphism in coumarin 7-hydroxylation, sequence of the human *CYP2A* genes and identification of variant *CYP2A6* alleles. *Am J Hum Genet* 1995; **57**:651–660.

Hiroi T, Imaoka S, Funae Y. Dopamine formation from tyramine by CYP2D6. *Biochem Biophys Res Commun* 1998; **249**:838–843.

Hirvonen A, Husgafvel-Pursiainen K, Anttila S, Karjalainen A, Pelkonen O, Vainio H. PCR-based *CYP2D6* genotyping for Finnish lung cancer patients. *Pharmacogenetics* 1993; **3**:19–27.

Ingelman-Sundberg M. Duplication, multiduplication and amplification of genes encoding drug metabolising genes. Evolutionary, toxicological and clinical pharmaceutical aspects. *Drug Metab Rev* 1999: **31**:445–459.

Johanson C-E, Fischman MW. The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 1989; **41**:3–52.

Johansson I, Lundqvist E, Bertilsson L, Dahl M-L, Sjöqvist F, Ingelman-Sundberg M. Inherited amplification of an active gene in the cytochrome P450 *CYP2D* locus as a cause of ultrarapid metabolism of debrisoquine. *Proc Natl Acad Sci USA* 1993; **90**:11825–11829.

Løvlie R, Daly AK, Molven A, Idle JR, Steen VM. Ultrarapid metabolizers of debrisoquine: characterization and PCR-based detection of alleles with duplication of the *CYP2D6* gene. *FEBS Lett* 1996; **392**:30–34.

McCullagh P, Nelder, JA, Generalized linear models. 2nd edn. London: Chapman and Hall, 1994.

Messina ES, Tyndale RF, Sellers EM. A major role for CYP2A6 in nicotine C-oxidation by human liver microsomes. *J Pharmacol Exp Ther* 1997; **282**:1608–1614.

Niznik HB, Tyndale RF, Sallee FR, Gonzalez FJ, Hardwick JP, Inaba T, Kalow W. The dopamine transporter and cytochrome P45OIID1 (debrisoquine 4-hydroxylase) in brain, resolution and identification of two distinct [3H]GBR-12935 binding proteins. *Arch Biochem Biophys* 1990; **276**:424–432.

Oscarson M, Gullstén H, Rautio A, Bernal ML, Sinues B, Dahl M-L, *et al*. Genotyping of human cytochrome P450 2A6 (CYP2A6), a nicotine *C*-oxidase. *FEBS Lett* 1998; **438**:201–205.

Pianezza ML, Sellers EM, Tyndale RF. Nicotine metabolism defect reduces smoking. *Nature* 1998; **393**:750.

Rostami-Hodjegan A, Lennard MS, Woods HF, Tucker GT. Meta-analysis of studies of the *CYP2D6* polymorphism in relation to lung cancer and Parkinson's disease. *Pharmacogenetics* 1998; **8**:227–238.

Saarikoski S, Voho A, Reinikainen M, Anttila S, Karjalainen A, Malaveille C, *et al*. Combined effect of polymorphic GST genes on individual susceptibility to lung cancer. *Int J Cancer* 1998; **77**:516–521.

Sachse C, Brockmöller J, Bauer S, Roots I, Cytochrome P450 2D6 variants in a Caucasian population: allele frequencies and phenotypic consequences, *Am J Hum Genet* 1997; **60**:284–295.

Smith CAD, Gough AC, Leigh PN, Summers BA, Harding AE, Maranganore DM, *et al*. Debrisoquine hydroxylase gene polymorphism and susceptibility to Parkinson's disease. *Lancet* 1992; **339**:1375–1377.

Stolerman IP, Shoaib M. The neurobiology of tobacco addiction. *TiPS* 1991; **12**:467–473.

Turgeon J, Labbe L, Lefez C, LeBel M. Debrisoquine metabolic ratio (DMR) distribution differs among smokers and non-smokers. *Clin Pharmacol Ther* 1995; **57**:150.

Woolverton WL, Johnson KM, Neurobiology of cocaine abuse. *TiPS* 1992; **13**:193–200.